SUSTAINED-RELEASE COMPOSITION, METHOD FOR PRODUCING THE SAME AND PREPARATION OF THE SAME

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Abstract of **JP2004075662**

PROBLEM TO BE SOLVED: To provide a sustained-release composition capable of obtaining the sustained-release effect for a long period by an injection of fine particles in an amount not causing pain subcutaneously or intramuscularly.

SOLUTION: This sustained-release composition is obtained by filling pores presenting in porous hydroxyapatite fine particles with a physiologically active medicine, human serum protein and mucopolysaccharide, and occluding by adding a divalent metal ion. Also, the composition is obtained by filling the pores presenting in the porous hydroxyapatite fine particles with the physiologically active medicine, the human serum protein and a water soluble calcium salt one by one or at once time and then occluding the outer layer of the fine particles by adding sodium carbonate, sodium hydrogen carbonate or an aqueous solution of carbonate ion.

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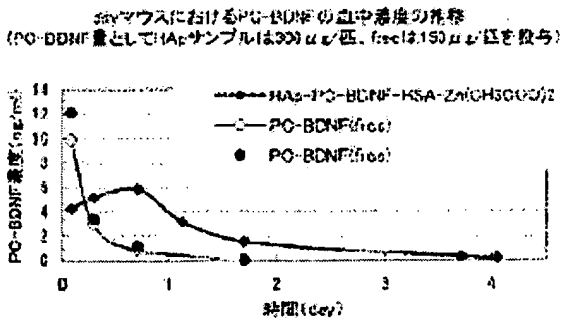

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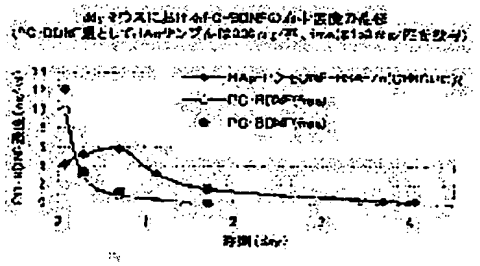
(54) SUSTAINED-RELEASE COMPOSITION, METHOD FOR PRODUCING THE SAME AND PREPARATION OF THE SAME

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a sustained-release composition capable of obtaining the sustained-release effect for a long period by an injection of fine particles in an amount not causing pain subcutaneously or intramuscularly.
SOLUTION: This sustained-release composition is obtained by filling pores presenting in porous hydroxyappatite fine particles with a physiologically active medicine, human serum protein and mucopolysaccharide, and occluding by adding a divalent metal ion. Also, the composition is obtained by filling the pores presenting in the porous hydroxyappatite fine particles with the physiologically active medicine, the human serum protein and a water



soluble calcium salt one by one or at once time and then occluding the outer layer of the fine particles by adding sodium carbonate, sodium hydrogen carbonate or an aqueous solution of carbonate ion.

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CLAIMS

[Claim(s)]
[Claim 1]
The sustained-release constituent characterized by coming to carry out plugging by filling up with biological activity drugs, Homo sapiens serum protein, and a mucopolysaccharide the pore which exists in a porous hydroxyapatite particle, and adding a divalent metallic ion.
[Claim 2]
The sustained-release constituent according to claim 1 characterized by for said porous hydroxyapatite particle spray-drying hydroxyapatite suspension, and calcinating at 100-800 degrees C.
[Claim 3]
The sustained-release constituent according to claim 1 or 2 characterized by the particle size of said porous hydroxyapatite particle being 0.1-20 micrometers.
[Claim 4]
The sustained-release constituent according to claim 1 characterized by the content in the sustained-release constituent of said biological activity drugs being at least 0.01 % of the weight.
[Claim 5]
The sustained-release constituent according to claim 1 characterized by said Homo sapiens serum protein being a human serum albumin or gamma globulin.
[Claim 6]
The sustained-release constituent according to claim 1 or 5 characterized by the content in the sustained-release constituent of said Homo sapiens serum protein being at least 1 % of the weight.
[Claim 7]
The sustained-release constituent according to claim 1 characterized by said divalent metallic ions being zinc ion, calcium ion, and magnesium ion.
[Claim 8]
The sustained-release constituent according to claim 1 or 6 characterized by the content in the sustained-release constituent of said divalent metallic ion being at least 0.01 % of the weight.
[Claim 9]
said mucopolysaccaride -- chondroitin sulfate, hyaluronic acid, heparin, a heparan sulfate, dermatan sulfate or keratan sulfates and those salts, and ** -- the

sustained-release constituent according to claim 1 characterized by being at least one sort inside.
[Claim 10]
The sustained-release constituent according to claim 1 or 9 characterized by the content in the sustained-release constituent of said mucopolysaccaride being 1/100 or more [of Homo sapiens serum protein].
[Claim 11]
A sustained-release constituent given in either of claim 1 to claims 10 characterized by being the gestalt to which said sustained-release constituent fitted subcutaneous injection, intradermal injection, an intramuscular injection, the administration in an eyeball, and skin spreading.
[Claim 12]
The sustained release drug characterized by consisting of having added the additive which can be received in galenical pharmacy to said constituent according to claim 1 if needed.
[Claim 13]
Pharmaceutical preparation according to claim 12 characterized by said additive which can be received in galenical pharmacy being a surfactant, antiseptics, or a stabilizing agent.
[Claim 14]
Pharmaceutical preparation characterized by freeze-drying said pharmaceutical preparation according to claim 12.
[Claim 15]
Pharmaceutical preparation given in either of claim 12 to claims 14 characterized by being the gestalt to which said pharmaceutical preparation fitted subcutaneous injection, intradermal injection, an intramuscular injection, the administration in an eyeball, and skin spreading.
[Claim 16]
The sustained-release constituent characterized by enough or freeze-drying whenever [middle], putting a divalent metallic ion solution into it, and coming to carry out plugging of the whole particle after filling up with biological activity drugs, Homo sapiens serum protein, and a mucopolysaccharide the pore which exists in a porous hydroxyapatite particle.
[Claim 17]
The sustained-release constituent characterized by coming to carry out plugging to the outer layer of this particle by filling up with biological activity drugs and Homo sapiens serum protein the pore which exists in a porous hydroxyapatite particle, and adding a divalent metallic ion.
[Claim 18]
The sustained-release constituent characterized by coming to carry out plugging of the outer layer of this particle by filling up with biological activity drugs, a human serum albumin, and a water-soluble calcium salt at ****** the pore which exists in a porous hydroxyapatite particle one after another again, and then adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution.
[Claim 19]
The sustained-release constituent according to claim 18 characterized by said

water-soluble calcium salts being a calcium chloride, calcium acetate, and a calcium nitrate.
[Claim 20]
The sustained-release constituent characterized by enough or coming to carry out plugging of the whole particle by freeze-drying whenever [middle] and then adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution after filling up with biological activity drugs, a human serum albumin, and a water-soluble calcium salt at ****** the pore which exists in a porous hydroxyapatite particle one after another again.
[Claim 21]
The sustained-release constituent characterized by coming to carry out plugging of the outer layer of a particle by filling up with biological activity drugs and a water-soluble calcium salt at ****** the pore which exists in a porous hydroxyapatite particle one after another again, and then adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution.
[Claim 22]
The sustained-release constituent characterized by making it come to combine hydroxyapatite and the high biological activity drugs of especially affinity with the inner surface of the pore which exists in a porous hydroxyapatite particle.
[Claim 23]
The sustained-release constituent characterized by coming to carry out plugging by combining biological activity drugs with the inner surface of the pore which exists in a porous hydroxyapatite particle, and adding a divalent metallic ion further.
[Claim 24]
The sustained-release constituent characterized by coming to carry out plugging by combining a divalent metallic ion with the inner surface of the pore which exists in a porous hydroxyapatite particle, and adding biological activity drugs further.
[Claim 25]
The sustained-release constituent according to claim 23 or 24 characterized by said divalent metallic ions being zinc ion, a copper ion, calcium ion, and magnesium ion.
[Claim 26]
The sustained-release constituent for the skins characterized by filling up a porous hydroxyapatite particle with quasi drugs, such as a skin disease remedy agent or sunscreen, with a base material, and coming to mix with this with ointment, a cream, and a lotion.
[Claim 27]
The manufacture approach of the sustained-release constituent characterized by mixing with the water solution which becomes a porous hydroxyapatite particle from biological activity drugs and Homo sapiens serum protein, stirring it, **(ing) suspension, mixing a mucopolysaccharide water solution and a divalent metallic ion solution to this, and being dissociated and produced.
[Claim 28]
The manufacture approach of the sustained-release constituent characterized by being produced by mixing with the water solution which consists of biological

activity drugs and Homo sapiens serum protein, stirring it, **(ing) suspension, mixing a mucopolysaccharide water solution and a divalent metallic ion solution to this, separating into a porous hydroxyapatite particle at it, and freeze-drying this further.

[Claim 29]

The manufacture approach of the sustained-release constituent characterized by being produced by mixing with the water solution which consists of biological activity drugs and Homo sapiens serum protein, stirring it, **(ing) suspension, mixing a mucopolysaccharide water solution to this, separating into a porous hydroxyapatite particle at it, adding the divalent metallic ion solution after freeze drying, and freeze-drying this further.

[Claim 30]

The manufacture approach of the sustained-release constituent characterized by mixing with the water solution which becomes a porous hydroxyapatite particle from biological activity drugs, Homo sapiens serum protein, and a water-soluble calcium salt, stirring it, **(ing) suspension, mixing a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution to this, and being dissociated and produced.

[Claim 31]

The manufacture approach of the sustained-release constituent characterized by being produced by it mixing with the water solution which consists of biological activity drugs, Homo sapiens serum protein, and a water-soluble calcium salt, stirring it to a porous hydroxyapatite particle, **(ing) suspension to it, separating into it, adding the sodium carbonate after freeze-drying this, a sodium hydrogencarbonate, or a carbonate ion water solution, and freeze-drying further.

[Claim 32]

The manufacture approach of the sustained-release constituent characterized by being produced by it mixing with the water solution which consists of biological activity drugs and a water-soluble calcium salt, stirring it to a porous hydroxyapatite particle, **(ing) suspension to it, separating into it, adding the sodium carbonate after freeze-drying this, a sodium hydrogencarbonate, or a carbonate ion water solution, and freeze-drying further.

[Claim 33]

The manufacture approach of the sustained-release constituent characterized by mixing with the water solution which becomes a porous hydroxyapatite particle from biological activity drugs, stirring it, **(ing) suspension, mixing a divalent metallic ion solution to this, and being dissociated and produced.

[Claim 34]

The manufacture approach of the sustained-release constituent characterized by mixing and stirring a divalent metallic ion solution to a porous hydroxyapatite particle, **(ing) suspension, mixing the water solution which becomes from biological activity drugs at this, and being dissociated and produced.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to the hydroxyapatite particle content sustained-release constituent which carried out plugging processing, its manufacturing method, and its pharmaceutical preparation pan in detail at the sustained-release constituent for the skins about the porous hydroxyapatite particle content sustained-release constituent, manufacturing method, and its pharmaceutical preparation.
[0002]
[Description of the Prior Art]
The gradual release pharmaceutical preparation for injection can also perform application to playback medicine, and the importance is increasing it recently. The sustained release drug by inorganic and the organic particle, a capsule, hydro gel, etc. is developed until now. The sustained-release injections over the long period of time of a water-soluble drug made the basis polylactic acid and a glycolic acid (PLGA) until now, and the many have been examined (for example, patent reference 1, patent reference 2, and patent reference 3 reference). Moreover, the making [into the basis]-PLGA containing human growth hormone (hGH) sustained-release microcapsule is reported (for example, nonpatent literature 1 reference). Moreover, the sustained-release microcapsule which made the basis PLGA containing RYUPURORERIN which is LHRH agonist is reported (for example, nonpatent literature 2 reference). PLGA has the property desirable as a basis of injections by the basis of the slaking property in the living body which hydrolyzes and disappears in the living body. However, although the organic solvent which dissolves it is used in case the sustained release drug which generally uses PLGA is manufactured, hGH denaturalizes in an organic solvent and a part deactivates. The fall of such activity not only spoils effectiveness, but it has the danger of also bringing a living body bad effect. Furthermore, if water solubility of hGH is high and PLGA pharmaceutical preparation is used, carrying out superfluous emission in early stages of administration will not be avoided. In addition, although use of hydro gel etc. is reported, the usual injection administration is difficult. That is, the thick needle with which impregnation of gel is attained must be used, and it is not desirable for a patient. Moreover, there is already a report about the sustained-release particle using the human growth hormone which are hydroxyapatite and

bioactive drugs (for example, nonpatent literature 3 and nonpatent literature 4 reference). However, all are the two-component systems and the particle diameter of an apatite is also 40 to 80 micrometers. Or it is difficult to inject greatly therefore with 200 micrometers, and the gradual release effectiveness in in vivo has it. [unknown] Moreover, the amount of hGH(s) (the amount of enclosure) which stuck to the apatite particle is also 1%. It was as small as the following. Furthermore, there were some to which a burst takes place in said sustained release drug, and there was a trouble in respect of either -- there are some from which organization is carried out and a bioavailability falls considerably, and there are some which are not decomposed completely in the living body, and super-gradual release cannot be expected.
[0003]
[Patent reference 1]
JP,11-286403,A (claim 1)
[Patent reference 2]
JP,2000-239104,A (claim 1)
[Patent reference 3]
JP,2002-326960,A (claims 13 and 15)
[Nonpatent literature 1]
Nature Medicine, 2: 795-799, 1996
[Nonpatent literature 2]
Chemical Pharmaceutical Bulletin, 36: 1095-1103, 1988
[Nonpatent literature 3]
H. Gautier et al: Journal of Biomedical Material Research, 40, 606-613, 1998
[Nonpatent literature 4]
J. Guicheux et al: Journal of Biomedical Material Research, 34, 165-170, 1997
[0004]
[Problem(s) to be Solved by the Invention]
Then, this invention persons tried production of the gradual release pharmaceutical preparation which carries out plugging of the space of the nano of a porous hydroxyapatite particle, in order to solve these troubles. First, since hydroxyapatite had little vital reaction nature, in examination to current, although there is no organization and it was based on how to burn, it dissolved completely hypodermically [weeks / two - five], and the bioavailability was also good, and a burst did not take place, either, but it discovered that the remarkable gradual release effectiveness was acquired by plugging concomitant use.
[0005]
Then, this invention is injection of this particle of an amount which moreover does not cause pain easily to hypodermically [of people] or intramuscular, and aims at offering the sustained-release constituent with which the gradual release effectiveness is acquired over a long period of time, its manufacturing method, its pharmaceutical preparation, and the sustained-release constituent for the skins.
[0006]
[Means for Solving the Problem]
In order to attain said purpose, the sustained-release constituent of this invention fills up with biological activity drugs (a macromolecule, low-molecular drugs), Homo

sapiens serum protein, and a mucopolysaccharide the pore which exists in a porous hydroxyapatite particle, and they come to carry out plugging by adding a divalent metallic ion.

[0007]

Moreover, the sustained-release constituent of this invention is enough or a thing which freeze-dries whenever [middle], puts a divalent metallic ion solution into it, and comes to carry out plugging of the whole particle, after filling up with biological activity drugs, Homo sapiens serum protein, and a mucopolysaccharide the pore which exists in a porous hydroxyapatite particle.

[0008]

Moreover, the sustained-release constituent of this invention fills up with biological activity drugs and Homo sapiens serum protein the pore which exists in a porous hydroxyapatite particle, and they come to carry out plugging to the outer layer of this particle by adding a divalent metallic ion.

[0009]

Moreover, the sustained-release constituent of this invention comes to carry out plugging of the outer layer of this particle by filling up with biological activity drugs, a human serum albumin, and a water-soluble calcium salt at ****** the pore which exists in a porous hydroxyapatite particle one after another again, and then adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution.

[0010]

Moreover, the sustained-release constituent of this invention is enough or a thing which comes to carry out plugging of this whole particle by freeze-drying whenever [middle] and then adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution, after filling up with biological activity drugs, a human serum albumin, and a water-soluble calcium salt at ****** the pore which exists in a porous hydroxyapatite particle one after another again.

[0011]

Moreover, the sustained-release constituent of this invention comes to carry out plugging of the outer layer of a particle by filling up with biological activity drugs and a water-soluble calcium salt at ****** the pore which exists in a porous hydroxyapatite particle one after another again, and then adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution.

[0012]

Moreover, the sustained-release constituent of this invention makes it come to combine hydroxyapatite and the high bioactive drugs of especially affinity with the inner surface of the pore which exists in a porous hydroxyapatite particle.

[0013]

Moreover, it comes to carry out plugging of the sustained-release constituent of this invention by combining bioactive drugs with the inner surface of the pore which exists in a porous hydroxyapatite particle, and adding a divalent metallic ion further.

[0014]

Moreover, it comes to carry out plugging of the sustained-release constituent of this invention by combining a divalent metallic ion with the inner surface of the

pore which exists in a porous hydroxyapatite particle, and adding bioactive drugs further.

[0015]

Moreover, the sustained-release constituent for the skins of this invention fills up a porous hydroxyapatite particle with quasi drugs, such as a skin disease remedy agent or sunscreen, with a base material, and comes to mix with this with ointment, a cream, and a lotion.

[0016]

Since the porous hydroxyapatite particle is filled up with this sustained-release constituent for the skins, a suitable amount is applied to the skin. Then, effectiveness will continue by that to which ultraviolet absorption matter, such as quasi drugs, such as a skin disease remedy agent with which an effective component will be gradually released gradually from a porous hydroxyapatite particle, and the porous hydroxyapatite particle is filled up, or sunscreen, oozes out gradually (that is, it releases gradually).

[0017]

The manufacture approach of the sustained-release constituent of this invention mixes and stirs the water solution which becomes a porous hydroxyapatite particle from biological activity drugs and Homo sapiens serum protein, ** suspension, mixes a mucopolysaccharide water solution and a divalent metallic ion solution to this, and is separated and produced.

[0018]

Moreover, it mixes with the water solution which consists of biological activity drugs and Homo sapiens serum protein, it is stirred, and suspension is **(ed), and a mucopolysaccharide water solution and a divalent metallic ion solution are mixed to this, it separates into a porous hydroxyapatite particle at it, and the manufacture approach of the sustained-release constituent of this invention is produced by freeze-drying this further.

[0019]

Moreover, it mixes with the water solution which consists of biological activity drugs and Homo sapiens serum protein, it is stirred, and suspension is **(ed), and a mucopolysaccharide water solution is mixed to this, it separates into a porous hydroxyapatite particle at it, and the manufacture approach of the sustained-release constituent of this invention is produced by adding the divalent metallic ion solution after freeze drying, and freeze-drying this further.

[0020]

Moreover, the manufacture approach of the sustained-release constituent of this invention mixes and stirs the water solution which becomes a porous hydroxyapatite particle from biological activity drugs, Homo sapiens serum protein, and a water-soluble calcium salt, ** suspension, mixes a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution to this, and is separated and produced.

[0021]

Moreover, it mixes with the water solution which consists of biological activity drugs, Homo sapiens serum protein, and a water-soluble calcium salt, it is stirred to a porous hydroxyapatite particle, suspension is **(ed) to it, it separates into it,

and the manufacture approach of the sustained-release constituent of this invention is produced after freeze-drying this by adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution, and freeze-drying further.

[0022]

Moreover, it mixes with the water solution which consists of biological activity drugs and a water-soluble calcium salt, it is stirred to a porous hydroxyapatite particle, suspension is **(ed) to it, it separates into it, and the manufacture approach of the sustained-release constituent of this invention is produced after freeze-drying this by adding a sodium carbonate, a sodium hydrogencarbonate, or a carbonate ion water solution, and freeze-drying further.

[0023]

Moreover, the manufacture approach of the sustained-release constituent of this invention mixes and stirs the water solution which becomes a porous hydroxyapatite particle from biological activity drugs, ** suspension, mixes a divalent metallic ion solution to this, and is separated and produced.

[0024]

Furthermore, the manufacture approach of the sustained-release constituent of this invention mixes and stirs a divalent metallic ion solution to a porous hydroxyapatite particle, ** suspension, mixes the water solution which becomes from biological activity drugs at this, and is separated and produced.

[0025]

It is suitable that said porous hydroxyapatite particle spray-dries hydroxyapatite suspension, and calcinates at 100-800 degrees C. It is because pore is crushed and it cannot calcinate below 100 degrees C, if it is 800 degrees C or more.

[0026]

It is suitable that the particle size of said porous hydroxyapatite particle is 0.1-20 micrometers.

[0027]

It is suitable that the content in the sustained-release constituent of said biological activity drugs is at least 0.01 % of the weight.

[0028]

It is suitable that said Homo sapiens serum protein is a human serum albumin or gamma globulin.

[0029]

It is suitable that the content in the sustained-release constituent of said Homo sapiens serum protein is at least 1 % of the weight.

[0030]

It is suitable that said divalent metallic ions are zinc ion, a copper ion, calcium ion, and magnesium ion.

[0031]

It is suitable that the content in the sustained-release constituent of said divalent metallic ion is at least 0.01 % of the weight.

[0032]

said mucopolysaccaride -- chondroitin sulfate, hyaluronic acid, heparin, a heparan sulfate, dermatan sulfate or keratan sulfates and those salts, and ** -- it is

suitable that it is at least one sort inside.
[0033]
It is suitable that the content in the sustained-release constituent of said mucopolysaccaride is 1/100 or more [of Homo sapiens serum protein].
[0034]
It is suitable that it is the gestalt to which said sustained-release constituent fitted subcutaneous injection, intradermal injection, an intramuscular injection, the administration in an eyeball, skin spreading, etc.
[0035]
Moreover, it is suitable for the sustained release drug of this invention to consist of having added the additive which can be received in galenical pharmacy to the aforementioned constituent if needed.
[0036]
It is suitable that said additive which can be received in galenical pharmacy is a surfactant, antiseptics, or a stabilizing agent.
[0037]
It is suitable that said pharmaceutical preparation is freeze-dried.
[0038]
It is suitable that it is the gestalt to which said pharmaceutical preparation fitted subcutaneous injection, intradermal injection, an intramuscular injection, the administration in an eyeball, skin spreading, etc.
[0039]
It is suitable that said water-soluble calcium salts are a calcium chloride, calcium acetate, and a calcium nitrate.
[0040]
Furthermore, the description of this invention is indicated below.
This invention consists of outer layer plugging and all layer plugging. First, it puts into the pore of porous hydroxyapatite with the matter and stabilizer which are used for plugging, and plugging is built with any case of the plugging approach for a chief remedy independent or by settling the above-mentioned constituent by adding a sodium carbonate, the matter, i.e., the divalent metallic ion, which produces precipitate, a sodium hydrogencarbonate, or a carbonate ion water solution. Or a divalent metallic ion is put into the pore of porous hydroxyapatite, adding the water solution of biological activity drugs subsequently and the water solution of biological activity drugs are put into the pore of porous hydroxyapatite, and plugging is made to form by subsequently adding a divalent metallic ion solution. When carrying out plugging only of the outer layer, after making it filled up with internal pore with a constituent, the quality of a precipitation ghost is added. When carrying out plugging of all the layers, it is being able to freeze-dry the particle containing a constituent once, being able to put air into pore, and being able to carry out plugging of all the layers, when a precipitation ghost's permeates even the interior of a particle.
[0041]
In addition, the thing for which the magnitude of a porosity hydroxyapatite particle, the size of a gap and an amount, and a suitable burning temperature are adding only zinc salt and a sodium carbonate at the end several times at the time of b

outer layer plugging method, Moreover, [that it is better whether to be filled up with drugs, protein, and the mucopolysaccaride as mixed liquor, and] [whether when it is better to add one by one or carries out plugging of the whole c, freeze drying is made perfect, it is / direction / good or whenever / middle / is good, and] d) -- or drugs presuppose on clinical that initial-complement enclosure is carried out and are good as optimum ratio, such as protein / mucopolysaccaride / zinc, and e mucopolysaccaride at chondroitin sulfate -- f depending on the property of a drug, plugging is possible only at a divalent metallic ion -- etc. -- it changes with each drugs.

[0042]

[Example]

Below, the example of this invention is described.

(Example 1)

The 4.54mg [/ml] PC-BDNF (lecithin-ized BDNF) solution was 66microl Added to 20mg (HAp) of porous hydroxyapatite particles calcinated at 180 degrees C, it stirred for 1 minute in the vortex, the HSA solution was 434microl Added to it 0.1%, and it stirred for 1 minute again. Since standing of them was carried out for 3 minutes, 1000rpm and centrifugal [for 3 minutes] were applied, supernatant liquid was collected, the 5mM Zn(CH3COO)2/5% Mannitol solution was 500microl Added and stirred to dregs, and the sample was prepared. It is 4.54mg/ml as control. The sample which made 66microl and 5%Mannitol mix with 434microl also prepared the PC-BDNF solution. 500microl administration of these was done hypodermically [of a 6 weeks old male ddy mouse], eye socket blood collecting was performed 2, 7 or 17 hours, and 1, 2, and 4 days [administration and] after, and the blood drug concentration of PC-BDNF was measured in ELISA KIT (Promega). The gradual release effectiveness which was excellent as a result was acquired. This result was shown in drawing 1 .

[0043]

(Example 2)

225microg/ml IFNalpha (interferon-alpha, Sumitomo Pharmaceuticals) 0.854 ml and 20mg/ml HSA 1.2ml were mixed, and protein mixed liquor was prepared. It is protein mixed liquor to HAp 200mg calcinated at 180 degrees C. It mixed with 0.856ml, it was stirred and protein was made to enclose with HAp. It is 20mg/ml to this. H 2O0.074 ml with a chondroitin sulfate (CS, WAKO) of 0.05 ml and 1M Zn (CH3COO)2 0.02ml were added in order. Centrifugal [of 15000rpm and 5min.] was performed, 2ml of 20mM Zn(CH3COO)2/5% Mannitol solutions was added to dregs, and it considered as the sample.

Control made H2O 0.644ml, 20% Mannitol 0.5ml, in addition this the solution of IFNalpha (free) at 0.856ml of protein mixed liquor containing IFNalpha.

The sample adjusted to the ddy mouse (weights 33-40g, SLC) of a 8-weeks old male above was administered hypodermically 0.5ml. Eye socket blood collecting was performed from the mouse 4 hours after administration and until after one - ten days, and blood was extracted. ELISA KIT (Biosource) showed measurement and the pharmacokinetics and metabolism in blood for the IFNalpha blood drug concentration of this blood to drawing 2 . And the outstanding gradual release effectiveness was acquired.

[0044]
(Example 3)
0.937mg/ml IFNalpha 0.06 ml, 20mg/ml HSA 0.3ml, 20mg/ml CS 0.03ml, and H2O 1.22ml were mixed, and HAp 200mg calcinated at 180 degrees C was made to act on this solution. After making stirring enclose protein with HAp, H2O 10ml was added, and it stirred lightly, and carried out centrifugal by 3000rpm and 5min. Dregs were equally freeze-dried and divided into two. The 20mM Zn(CH3COO)2/5% Mannitol solution was added to one side, and 1ml of 5mM Zn(CH3COO)2/5% Mannitol solutions was added to 1ml and another side.
As control, it is 0.937mg/ml IFNalpha. It adjusted as a solution of 0.015 ml, 20mg/ml HSA 0.075ml, H2O 0.66ml, 20% Mannitol 0.25ml, in addition IFNalpha (free).
The sample adjusted to the ddy mouse (weights 31-33g, SLC) of a 7-weeks old male above was administered hypodermically 0.7ml. Eye socket blood collecting was performed from the mouse 4 hours after administration and until after one - seven days, and blood was extracted. ELISA KIT (Biosource) showed measurement and the pharmacokinetics and metabolism in blood for the IFNalpha blood drug concentration of this blood to drawing 3 . When a result and zinc were 20mM(s), although the rise of blood drug concentration was inadequate, gradual release was remarkably shown over the long period of time. On the other hand, when zinc was 5mM(s), although the rise of blood drug concentration was good, blood drug concentration fell to whether you are Sumiya comparatively.
[0045]
(Example 4)
G-CSF and HSA with which it mixed beforehand, and CaCl2 solution (3microg, 30microg, and 280mg/(ml)) were 100microl Added to HAp50mg calcinated at 180 degrees C, in the vortex, it stirs for 3 minutes, standing was carried out for 5 minutes, and it freeze-dried. 220mg [/ml] Na2CO3 solution was 100microl Added to the obtained particle, it stirred for 3 minutes in the vortex, 100micro of water l was added further, and it stirred lightly. The part was extracted to ELISA measurement, 1000rpm and centrifugal [for 3 minutes] were applied for the remainder, PBS 2ml was added to recovery and dregs, supernatant liquid was lightly shaken at the room temperature, and supernatant liquid was collected 0 hour and 0.5 hours after, respectively. The supernatant liquid which furthermore added PBS 10 ml to the dregs, shook at the room temperature, and was obtained by the middle with the dregs of recovery and the last in supernatant liquid 0 hour and 0.5 hours after, respectively was measured by ELISA KIT (IBL). It dissolved in BSA/Tris-HCl (pH5) 1%, and the last dregs carried out to ELISA measurement. This result was shown in drawing 4 -A. Moreover, it is G-CSF of g/ml 1.5micro to HAp 50mg. The solution was 200microl Added, it was filled up with porosity, PBS was added further 2 ml, and the result of having performed the emission trial similarly was shown in drawing 4 -B. Thus, emission was remarkably suppressed by the plugging technique.
[0046]
(Example 5)
HAp50mg calcinated at 180 degrees C -- a 100mg [/ml] SOD solution -- 10microl

or a 40mg [/ml] PC-SOD (lecithin-ized SOD) solution -- 25microl -- adding -- a vortex -- for 1 minute -- stirring -- it -- water -- 990microl -- or 975microl in addition, it stirred for 1 minute again. Since standing of them was carried out for 3 minutes, 1000rpm and centrifugal [for 3 minutes] were applied, supernatant liquid was collected, 2ml of water was added and stirred to dregs, 1000rpm and centrifugal [for 3 minutes] were applied, supernatant liquid was added to recovery and a pan, PBS 2ml was added to the dregs, it stirred, 1000rpm and centrifugal [for 3 minutes] were applied, and supernatant liquid was collected. PBS 1ml was added to the dregs obtained now, it shook at the room temperature, supernatant liquid was collected 0 hour and 1 hour after, respectively, and the dregs of supernatant liquid and the last were measured by BCA assay (PIERCE). The result was shown in drawing 5 . Thus, by chemical modification, there is protein which the amount of adsorption to HAp increases.

[0047]

(Example 6)

6ml of Mannitol(s) was added to HAp 24mg calcinated at a freeze-drying article, 180 degrees C, and 800 degrees C 5%, it stirred for 1 minute by the vortex, and the HAp solution was adjusted. The three backs of the Wistar rat (weight of 330.400g and SLC) of a 13-weeks old male were medicated with each HAp solution every [500micro / l] so that the location prescribed for the patient might not lap. The back was cut open for these 2 hours and 4, 7, 11, 14, 18, and 21 days after, and the amount of survival of HAp was photoed with the photograph. Later, several persons estimated the near amount of survival by the eye with the photograph. Consequently, each HAp could not disappear easily, so that burning temperature was high, although it disappeared in about 2-3 weeks. This result was shown in drawing 6 .

[0048]

(Example 7) Adsorption to the hydroxyapatite of G-CSF through zinc

After dipping a 40mg hydroxyapatite particle for 10 minutes into 100micro (100microg/(ml)) of G-CSF solutions l, the purified water of 900microl was added and superfluous G-CSF was removed for stirring and after [centrifugal separation] supernatant liquid **** and by stirring and carrying out centrifugal separation of the precipitate with purified water again. Precipitate was suspended in the acetic-acid buffer solution of pH4, and when elution of G-CSF was carried out, the amount of G-CSF of after [centrifugal separation] supernatant liquid was measured by ELISA and the amount of adsorption of G-CSF was calculated, adsorption was hardly seen below 0.1microg.

Then, zinc was made to stick to a hydroxyapatite particle by the following actuation, and G-CSF adsorption was tried to the particle. At-long-intervals alignment separation and supernatant liquid were thrown away into the zinc acetate (5mg/(ml)) of 200microl for 10mg hydroxyapatite by 10,000rpm after neglect for suspension and 10 minutes for 10 minutes at the room temperature. Precipitate was suspended with the purified water of 500microl, and at-long-intervals alignment separation and supernatant liquid were thrown away into the room temperature by 10,000rpm after neglect for 10 minutes for 10 minutes. Again, supernatant liquid was thrown away after suspension and centrifugal separation.

This precipitate was suspended in the 0.5ml G-CSF (200microg [// ml] or 1000microg/ml) solution, at-long-intervals alignment separation was carried out by 10,000rpm after neglect for 10 minutes for 10 minutes, and the amount of G-GSF of supernatant liquid was measured by the ELISA method. Furthermore elution of G-CSF contained in hydroxyapatite with 0.1MEDTA(s) and 1%HAS solution in precipitate was carried out, the G-CSF concentration of after [centrifugal separation] supernatant liquid was measured by the ELISA method, and the amount of adsorption to hydroxyapatite was calculated.
80.0 - 86.4% of G-CSF added to 10mg hydroxyapatite adsorbed by processing hydroxyapatite with zinc salt beforehand, as shown in Table 1.
G-CSF of 400micro[a maximum of] g was able to be made to stick to 10mg hydroxyapatite.

表1　亜鉛を結合させたハイドロキシアパタイト（10mg）へのG-CSFの吸着量

ハイドロキシアパタイト量（mg）	G-CSF全量（μg）	G-CSF非吸着量（μg）	G-CSF吸着量（μg）
10	100	0.4	86.4
10	500	90.0	400.0

[0049]
(Example 8)
45mg (HAP) of porous hydroxyapatites was weighed precisely, 30microg was added to it as IFN from 2.4mg [/ml] solution of interferon alpha (IFN), and it was left for 10 minutes. Then, 20mM(s) / 1ml of 1ml zinc acetate solutions was added to this, and it shook for 30 minutes. IFN was not detected, when 1.5ml water was added and washed to these dispersion liquid and the quantum of the inside IFN of a penetrant remover was carried out. That is, it was checked that all IFN(s) are sticking to HAP. Thus, the particle pharmaceutical preparation which adsorbed IFN which is protein without using an organic solvent was able to be obtained. 20ml of PBS solutions of FCS content was added to the powder obtained after washing 20%, and it shook at 37 degrees C for 16 hours. The rate of elution was computed by having carried out the quantum of the IFN eluted in supernatant liquid. The result shown in Table 2 was obtained.

表2　HAPに吸着したIFNの溶出率

		溶出したIFN(%)
HAP	酢酸亜鉛　0mM	92
	酢酸亜鉛 20mM	87

Elution was controlled by addition of zinc acetate and showed sustained-release [covering long duration] more by it as compared with additive-free.

[Brief Description of the Drawings]

[Drawing 1] It is drawing showing transition of the blood drug concentration of PC-BDNF after the PC-BDNF-HAp pharmaceutical preparation administration in a ddy mouse.

[Drawing 2] It is drawing showing transition of after [IFN alpha-HAp pharmaceutical preparation administration] ddy mouse IFNalpha blood drug concentration.

[Drawing 3] Zn concentration is drawing showing the effect which it has on gradual release of IFN-HAp pharmaceutical preparation.

[Drawing 4] It is drawing showing the difference in association to HAp of G-CSF by ** and nothing. [of plugging]

[Drawing 5] in It is drawing showing the drugs elution result in vitro.

[Drawing 6] It is drawing showing the comparison of solubility in the living body by the difference in burning temperature.

[Translation done.]

* NOTICES *

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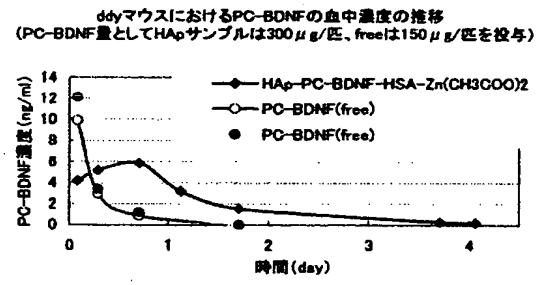
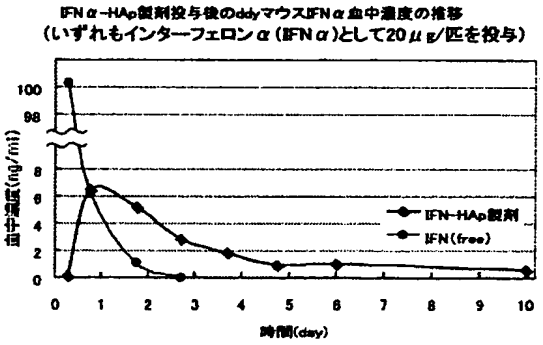
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DRAWINGS

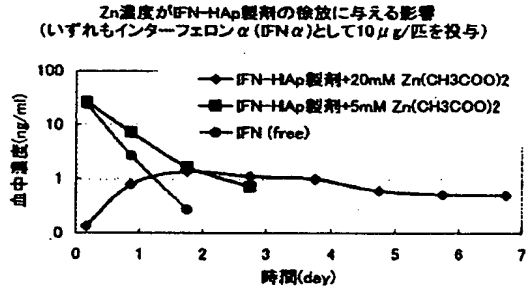
[Drawing 1]



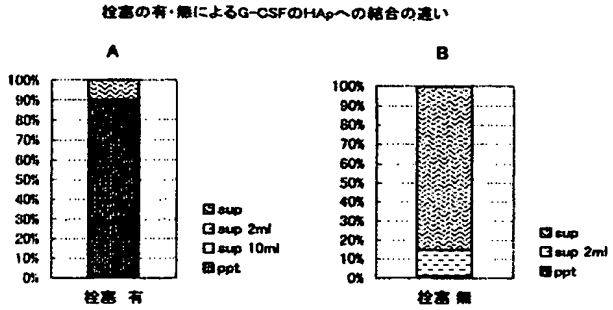
[Drawing 2]



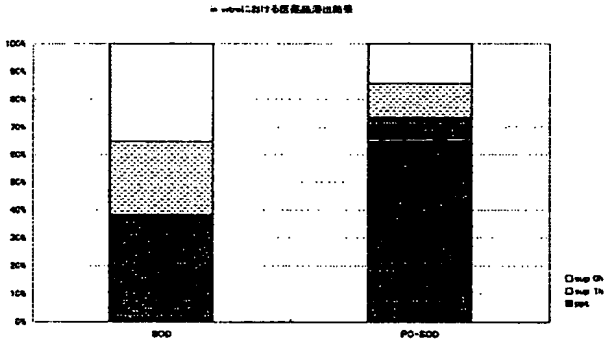
[Drawing 3]



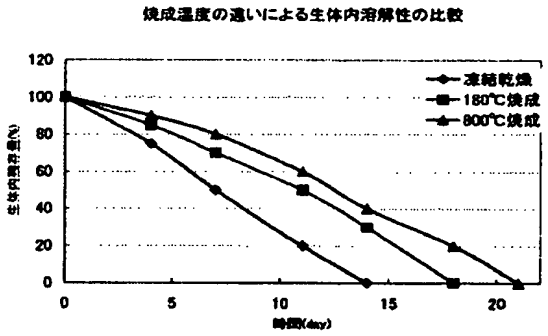
[Drawing 4]



[Drawing 5]



[Drawing 6]



[Translation done.]